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REVIEW ARTICLE

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Abiraterone acetate in the treatment of patients with metastatic prostate cancer

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ABSTRACT

For a long time, systemic treatment of patients diagnosed with metastatic castration-resistant prostate cancer (mCRPC) has been based solely on chemotherapy (docetaxel). The introduction of novel endocrine agents has significantly improved outcomes of mCRPC patients. Till date, abirateron acetate is the only drug with confirmed activity (significant improvement in overall survival) in both clinical settings: castration resistance (pre or post chemotherapy) and castration sensitivity. The article is aimed to summarize current knowledge on the place and role of abiraterone acetate in palliative systemic treatment of metastatic prostate cancer patients.

Key words: prostate cancer, abiraterone, castration resistance, metastases, endocrine treatment

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Introduction

The treatment of patients with disseminated castration-resistant prostate cancer (CRPC) has undergone a huge evolution over the last decade. In 2004, based on the results of the TAX327 study, docetaxel was registered, which significantly improved the prognosis of patients with metastatic CRPC compared to the current standard of chemotherapy — mitoxantrone, reducing the relative risk of death by 21% [1]. In the years following the introduction of docetaxel into clinical practice, numerous clinical trials have been initiated on new strategies of systemic treatment for patients with CRPC. These studies have been conducted in two main directions: (i) increasing the effectiveness of docetaxel-based chemotherapy by combining it with other drugs and (ii) developing active treatment options for patients after chemotherapy failure. In order to improve the effectiveness of docetaxel in the treatment of CRPC patients, attempts were made to combine this drug with bevacizumab, aflibercept, dasatinib (Src kinase inhibitor), zibotentan (ETA receptor inhibitor), or calcitriol [2–6]. Apart from a marked increase in treatment-related toxicity, none of above studies has shown significant improvement in prognosis. However, successful research on new strategies for systemic treatment of CRPC patients following the failure of docetaxel-based chemotherapy has led to the registration of several new drugs — hormone (abiraterone acetate — 2011 and enzalutamid — 2012), chemotherapy (cabazitaxel — 2010), and radioisotope (alpharadin — 2013).

Significant improvement of systemic treatment effectiveness for prostate cancer patients in the following years has been reported in patients with metastatic CRPC not previously treated with chemotherapy as well as in patients with primary disseminated cancer. As a result of performed studies abiraterone and enzalutamid were registered for the treatment of patients with metastatic CRPC, who had not previously undergone chemotherapy. In contrast, docetaxel, in combination with pharmacological castration, has become a standard treatment for patients with primary disseminated prostate cancer.

Among new systemic therapies registered for treatment of prostate cancer patients, to date only abiraterone acetate has obtained reimbursement status in Poland under the therapeutic drug program. This drug is currently the only hormone available with clearly

proven activity at various stages of metastatic prostate cancer. The aim of this article is to summarise current evidence on the role and place of abiraterone acetate in the treatment of patients with advanced prostate cancer.

Mechanism of action of abiraterone acetate

Abiraterone is a selective inhibitor of cytochrome P450 c17 (CYP17), an enzyme having 17α-hydroxylase and C17,20-lyase activity. CYP17 is essential for the biosynthesis of androgens in the testes, adrenal glands, and prostate cancer cells. Abiraterone inhibits androgen biosynthesis at the stage of pregnenolone and progesterone metabolism and leads to decrease in synthesis of testosterone and thus 5-α-dihydrotestosterone inducing proliferation of prostate cells. Abiraterone reduces testosterone and other androgen serum levels more than LHRH analogues or orchidectomy. Thus, the use of this drug by definition overcomes the resistance of prostate cancer cells to androgen deprivation. As a result of inhibition of CYP17 activity and reduction of glucocorticoid synthesis, ACTH level increases, resulting in increased synthesis of mineralocorticosteroids in adrenal glands. The excess of mineralocorticosteroids leads in turn to abiraterone-typical side effects — hypertension, hypokalaemia, and fluid retention. The use of glucocorticosteroids [prednisone 10 mg/d (divided dose)] reduces ACTH concentration and prevents the onset of the aforementioned undesirable effects. The mechanism of action of abiraterone is similar to that of ketoconazole, which was sometimes used in subsequent hormonal lines. However, the use of ketoconazole in the treatment of CRPC was characterised by low clinical activity with relatively high toxicity [7, 8].

Abiraterone acetate in the treatment of CRPC after chemotherapy

In their first phase, the studies on the role and place of abiraterone in the treatment of advanced prostate cancer patients were focused on the patient population after failure of docetaxel-based chemotherapy.

The phase III COU-AA-301 study involved 1195 patients with metastatic CRPC, who developed disease progression (biochemical or radiological) during or after discontinuation of docetaxel-based chemotherapy. Patients in ECOG performance status (PS) 0–2 and under continuous pharmacological castration were randomly assigned (2:1) to either the experimental arm [abiraterone 1000 mg/d + prednisone 10 mg/d (divided dose)] or the control group [placebo + prednisone 10 mg/d (divided dose)]. The study primary endpoint was overall survival (OS). The use of abiraterone was associated with a significant reduction in relative risk of death by 26% (HR = 0.74; 95% CI 0.64–0.86), and median OS was 15.8 months and 11.2 months in the abiraterone and placebo group, respectively.

Abiraterone significantly reduced the relative risk of biochemical progression by 42% ($p < 0.001$) and radiological progression by 33% ($p < 0.001$), also increasing the radiological response rate in patients with measurable lesions from 3% to 14% and biochemical lesions from 6% to 29% [9, 10].

Based on the FACT-P (Functional Assessment of Cancer Therapy — Prostate) questionnaire, the COU-AA-301 study demonstrated the beneficial effect of abiraterone on patients' quality of life both in terms of improvement of initially reduced parameters as well as delaying significant deterioration in quality of life [11].

Abiraterone acetate in the treatment of CRPC before chemotherapy

The natural consequence of demonstration of abiraterone activity in the treatment of patients after chemotherapy failure was a study evaluating the efficacy of this drug in a population of CRPC patients not previously receiving docetaxel. The COU-AA-302 study involved 1088 asymptomatic or oligosymptomatic patients with metastatic CRPC, in ECOG PS 0–1, without systemic metastasis. Patients were randomly assigned (1:1) to a group receiving either abiraterone + prednisone or placebo + prednisone. The first published study analysis demonstrated a significant increase in median radiographic progression-free survival (rPFS) — 16.5 months *vs.* 8.3 months in the abiraterone and placebo arm, respectively, which transferred into a reduction in risk of progression or death by 47% in the abiraterone arm (HR = 0.53; 95% CI 0.45–0.62) [12]. The use of abiraterone significantly reduced the risk of PS (18%) and quality of life (22%) deterioration as well as occurrence of pain requiring opioids (32%), prolonging the time to chemotherapy initiation (from 16.8 months to 25.2 months). Abiraterone significantly increased the percentage of patients with biochemical (62% *vs*. 24%) and radiological response (36% *vs*. 16%). Due to the fact that 44% of patients (n = 238) in the placebo arm received abiraterone after progression of disease, the final assessment of the effect of the drug on patients' overall survival required the use of the iterative parameter estimation (IPE) method. The final survival analysis was performed after a median follow-up of 49.2 months and 96% of expected survival events (741 deaths) [13]. Taking into account the impact of cross-over procedure, the use of abiraterone was associated with a significant decrease (by 19%) in relative risk of death in patients

with metastatic CRPC (HR = 0.81, 95% CI 0.70–0.93). OS median was 34.7 months and 30.3 months in abiraterone and placebo group, respectively.

The use of abiraterone acetate in patients with metastatic CRPC, who had not previously undergone chemotherapy, was associated with a typical and acceptable toxicity profile and a positive effect on their quality of life [14].

In a retrospective analysis of the COU-AA-301 study, the greatest benefit of abiraterone for overall survival was observed in asymptomatic patients in very good performance status.

Abiraterone acetate in disseminated castration-sensitive prostate cancer

The CHAARTED and STAMPED studies have shown a significant improvement in prognosis of patients with primary disseminated prostate cancer as a result of hormone therapy and chemotherapy administered together (androgen deprivation in combination with six docetaxel courses) compared to pharmacological castration alone [15–17]. The combination of hormone therapy and chemotherapy is now recognised as standard practice in previously untreated patients with extensive metastatic cancer, at the stage of potential sensitivity to castration.

In June 2017, the results of the phase III LATITUDE and STAMPEDE studies evaluating the clinical effect of abiraterone acetate (+ prednisone) in combination with pharmacological castration in patients with primary disseminated prostate cancer were published [17, 18]. The LATITUDE study included 1199 patients in ECOG PS 0–2 with newly diagnosed (≤ 3 months) generalised prostate cancer without the features of neuroendocrine or microcellular differentiation. In all patients, it was necessary to acknowledge the spread of tumour process and to demonstrate at least two of three high-risk criteria: (i) Gleason score ≥ 8, (ii) at least three metastatic bone lesions, (iii) measurable internal metastasis. Patients were randomly assigned to receive abiraterone in combination with androgen deprivation or to the arm receiving placebo together with androgen deprivation. First interim analysis of primary endpoints showed a significant reduction in relative risk of death by 38% and radiological progression by 53%. The three-year survival rate was 66% *vs.* 49% (HR = 0.65; 95% CI 0.51–0.76) and median rPFS 33.0 *vs*. 14.8 months (HR = 0.47; 95% CI 0.39–0.55) in the abiraterone and placebo arm, respectively [18].

In the multi-arm, multi-stage STAMPEDE study, the data from 1917 patients were analysed, assigned (1:1) to an experimental [Androgen-Deprivation Therapy (ADT) + abiraterone for two years] or control arm (ADT alone). Unlike LATITUTE, to the STAMPEDE study not only were previously untreated patients in stage IV qualified, but also patients in stage III or stage II with coexisting risk factors and patients with recurrence of disease after surgery or radiotherapy. The combination of abiraterone with ADT was associated with a significant reduction in relative risk of death in the general patient population by 37% (HR = 0.67; 95% CI 0.52–0.76) with an increase in the three-year survival rate from 76% (ADT) up to 83% (abiraterone + ADT). The three-year treatment failure-free survival rate was 75% (abiraterone + ADT) and 45% (ADT), which translated into a 70% reduction in the risk of treatment failure (HR = 0.29; 95% CI 0.25–0.34). In turn, the risk of radiological progression was reduced in the abiraterone receiving arm by 60% ($p < 0.001$). Retrospective subgroup analyses for overall survival suggest no superiority of combination therapy compared to androgen deprivation alone in patients at the age of ≥ 70 years despite a clear reduction in the risk of treatment failure [19].

The safety profile of combination therapy with abiraterone + ADT was similar in the LATITUDE and STAMPEDE studies, with clearly higher proportions of adverse events in 3–4 degrees according to CTCAE in the experimental arms.

Summary

The COU-AA-301 and COU-AA-302 studies, as well as the recently published LATITUDE and STAMPEDE studies, clearly point to the significant role of abiraterone acetate in the armamentarium of drugs used for treatment of patients with disseminated prostate cancer. With regard to neoplastic process at sensitivity-to-castration stage, abiraterone dramatically increases the activity of classical castration-based hormone therapy. At the time being it is difficult to judge which strategy — chemotherapy together with hormone therapy (ADT + docetaxel) or combination hormone therapy (ADT + abiraterone) — is a better therapeutic option. Most likely, due to differences in safety profiles (18 weeks of chemotherapy versus at least 24 months of therapy with abiraterone), different treatment strategies will be used for different patients. The comparison of ADT + abiraterone with ADT + docetaxel, expected within the multi-arm STAMPEDE study, should provide extremely interesting information.

However, there is no doubt that at present the key role of abiraterone is the treatment of patients with disseminated prostate cancer at the stage of castration resistance. In the vast majority of cases, progression of disease with post-castration testosterone levels results from androgen receptor stimulation by androgens produced in tissues being out of control by the hypothalamic-pituitary system. Abiraterone system-

atically inhibits androgen biosynthesis, thus completely blocking the possibility of stimulating the androgen receptor through this group of sex hormones, and the progression of disease during treatment with abiraterone is a typical hormonal resistance phenomenon. Considering potential abiraterone use both before and after docetaxel-based chemotherapy, the key issue in clinical practice is which strategy — chemotherapy or hormone therapy — should be used first. Abiraterone appears to be the first-line option in asymptomatic or oligosymptomatic patients with metastatic CRPC in good performance status (ECOG 0–1) without systemic metastases. In turn, docetaxel should be used in the first-line setting in patients with metastatic CRPC, who experience metastases in internal organs or severe disease-related symptoms. Scores of Gleason's scoring system for degree of malignancy < 8, which is postulated by some researchers as a potential indication for use of abiraterone in first-line treatment of CRPC patients, should not be used in the decision-making process. This is due to the fact that to date no correlation between the degree of malignancy and efficacy of abiraterone has been confirmed [20].

In clinical practice, however, one should always pay attention to the nature of disease progression after failure of new-generation hormone drugs (abiraterone, enzalutamide). As a consequence of complete blockade of hormone-dependent signal transduction, these drugs force the activation of numerous adaptive mechanisms in tumour cells, including loss of adenocarcinoma phenotype. The appearance of organ metastases, change of bone metastases nature from osteosclerotic to osteolytic, absent/slight biochemical progression with marked imaging/clinical progression, and elevated carcinoembryonic antigen (CEA) level, may be indicative of neuroendocrine differentiation of cancer cells [21]. Since the new-generation hormone drugs are commonly used, the phenomenon of neuroendocrine differentiation is increasingly observed; such clinical situations require the use of platinum-containing chemotherapy regimens (e.g. docetaxel + carboplatin) [22].

The introduction of new-generation hormone drugs has greatly improved the prognosis of patients with disseminated castration-resistant prostate cancer. However, there is no doubt that the place of these drugs in clinical practice will continue to evolve, and the best proof of it is the possibility of using abiraterone still at the stage of castration-sensitive cancer.

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